Universidade de Lisboa

Faculdade de Farmácia

Cannabis sativa: legalization, commercialization and medicinal use

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Kateline Duarte Cardoso

Mestrado Integrado em Ciências Farmacêuticas

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Monografia de Mestrado Integrado em Ciências Farmacêuticas apresentada à Universidade de Lisboa através da Faculdade de Farmácia

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2019

To my parents Octávio and Anita

To my grandmother Lúcia

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Abstract

Although primarily used today as one of the most prevalent illicit leisure drugs, the use of *Cannabis sativa* L., also referred to as marijuana, for medicinal purposes has been used since thousands of years ago. In Portugal it is legal for medicinal purpose since June 2018 and there is in fact cannabis production for medicinal purposes. However, cannabis use has been shown to create numerous health problems, and, consequently, the expanding use beyond medical purposes into recreational use resulted in debates wildly discussing whether its use as so should be legal or not.

Cannabis is among the very oldest of economic plants providing humans with fibre for weaving cloth and making paper; seed for human and animal feeds; and aromatic resin containing compounds of recreational and medicinal value.

Though, the effects of cannabis are extremely unpredictable as since they are conditioned by several factors. The long-term use of cannabis may also increase the risk of schizophrenia, paranoia, and other psychoses.

On the other hand, cannabis plants produce many compounds of possible medical importance, that is why cultivars with specific chemical profiles are being developed for diverse industrial and pharmaceutical uses. Conversely, innovative classical breeding techniques have been used to improve recreational drug forms of cannabis, resulting in many cannabinoid-rich cultivars suitable also for medicinal use.

The political climate surrounding medical cannabis legislation has become more informed, empathetic and tolerant. Cannabis cultivation for personal medical use will eventually become legalized or tolerated in many jurisdictions. If not by the public openly favouring legalization, then by increasing governmental awareness of the inefficiency inherent in attempted prohibition of a popular and effective medicine, when used properly.

Pharmaceutical research companies are developing new natural cannabinoid formulations and delivery systems that will meet government regulatory requirements. Moreover, clinical trials prove successful and the understanding of cannabis's efficacy and safety as a modern medicine spread. Therefore, patients can look forward to a steady flow of new medicines providing effective relief from a growing number of indications.

Keywords: *Cannabis sativa*; cannabinoids; medicinal cannabis; recreational cannabis; legalization.

Resumo

Ainda que atualmente seja usada principalmente como uma das drogas ilícitas de lazer mais prevalentes, o uso de *Cannabis sativa* L., também conhecida como marijuana, para fins medicinais, é usado há milhares de anos. Em Portugal, é legal para fins medicinais desde junho de 2018 e, de facto, existe produção de marijuana para uso medicinal no país. No entanto, o uso de canábis tem demonstrado criar inúmeros problemas de saúde, consequentemente, a expansão do uso para fins recreativos, resultou em debates discutindo amplamente se seu uso como tal deveria ser legalizado ou não.

A canábis está entre as plantas com relevância económica mais antigas, fornecendo ao Homem fibras para tecer tecidos e fabricar papel; sementes para alimentação humana e animal; não esquecendo da resina aromática que contém compostos de valor recreativo e medicinal.

No entanto, os efeitos da canábis são extremamente imprevisíveis, dado serem condicionados por variados fatores. É importante referir que o uso prolongado de canábis também pode aumentar o risco de esquizofrenia, paranoia e outras psicoses.

Por outro lado, a canábis produz muitos compostos de possível importância médica, assim sendo, existem cultivos com perfis químicos específicos que estão a ser desenvolvidos para diversos usos industriais e farmacêuticos. Para além disso, técnicas clássicas inovadoras de seleção genética têm sido usadas para aprimorar a quantidade de canabinóides.

O ambiente político em torno da legislação da canábis medicinal tem-se tornado cada vez mais informado, empático e tolerante. Pensa-se já que o cultivo de canábis para uso medicinal pessoal acabará por ser legalizado ou então tolerado em muitas jurisdições.

Muitas empresas da indústria farmacêutica estão a pesquisar e desenvolver novas formulações naturais de canabinóides, incluindo sistemas de administração que atenderão aos requisitos regulamentares do governo. Para além disso, muitos ensaios clínicos têm tido resultados positivos, o que prova um melhor conhecimento da eficácia e segurança da canábis como uma alternativa medicinal. Portanto, os pacientes podem esperar um fluxo constante de novos medicamentos, proporcionando alívio eficaz de um número crescente de indicações.

Palavras-chave: *Cannabis sativa*; canabinóides; canábis medicinal; canábis recreativa; legalização

Abbreviations

THC – Δ^9-tetrahydrocannabinol

CBD – Cannabidiol

DEA – Drug Enforcement Administration

GABA – γ-aminobutyric acid

CBDA – Canabidiol acid

CBDV – Cannabidivarin

THCA – The acid form of THC

THCV – Tetrahydrocannabivarin

THCVA – Tetrahydrocannabivarin acid form

CBG – Cannabigerol

CBGA – Cannabigerol acid form

CBN – Cannabinol

CBC – Cannabichromene

PTSD – Post-traumatic stress disorder

SICAD – Serviço de Intervenção nos Comportamentos Aditivos e nas Dependências

WHO – World Health Organization

Introduction and Objectives

There are many uncertainties about the health consequences of cannabis use. The research literature stays that potential harms do exist. On the other hand, cannabis plants produce many compounds with biological and pharmacological activities that have effect on different types of diseases, some with no prospect of cure.

Using cannabis for medicinal purposes raises legal, regulatory, and other practical issues. If the evidence does support medicinal use of cannabis, enabling patient access raises complex questions of supply and its organisation within the usual processes of the healthcare system, as well as problems of legally distinguishing medicinal from non-medicinal usage (1).

The understanding of the effects of policy on market forces is quite limited (the allure of new tax-revenue streams from the legal sale of marijuana, pricing wars, youth-targeted advertising, and the emergence of cannabis-based medicines approved by the Food and Drug Administration) (2). Moreover, there is a general uncertainty of the significance of cannabis potency, or THC content, the principal psychoactive component of cannabis, on health outcomes (3).

It is obvious that the use of any medication should be based on the clinical evidence of safety and efficacy. To acknowledge whether cannabis should be used medicinally, it is needed to know if cannabis is a safe and effective treatment for conditions, or if it is associated with significant adverse effects, and how it compares to other treatments for those specified conditions. The high and increasing prevalence of medical marijuana consumption in the general population invites the need for quality evidence regarding its safety and efficacy (4).

It is important to access whether botanical cannabis displays herbal synergy of its components, pharmacokinetics of cannabis and dose titration, whether cannabis medicines produce cyclo-oxygenase inhibition, cannabis-drug interactions, and cytochrome P450 issues, whether cannabis randomized clinical trials are properly blinded, combatting the placebo effect in those trials via new approaches, the drug abuse liability of cannabis-based medicines and their regulatory scheduling, their effects on cognitive function and psychiatric sequelae, immunological effects, cannabis and driving safety, youth usage, issues related to cannabis smoking and vaporization, cannabis concentrates and vape-pens, and laboratory analysis for contamination with bacteria and heavy metals. The issue of pesticide usage on cannabis crops should be also addressed (5).

About recreational cannabis use, what has been noticed is that the potency of the street cannabis available in many Western countries has increased not to mention that higher potency types of cannabis carry more risk than traditional forms. In the 1960s, herbal cannabis, marijuana, and resin, hashish, commonly contained 3% or less THC. However, by the early years of the 21st century, the mean THC had risen to 16% and 20% in England and Holland respectively. Early onset of use, daily use of high-potency cannabis, and synthetic cannabinoids carry the greatest risk. Many case-controlled studies showed that people using high-potency cannabis on a daily basis were five times more likely than non-users to suffer from a psychotic disorder, being this one of most common side effects of non-medical cannabis use. Prospective epidemiological studies have consistently demonstrated that cannabis use is associated with an increased subsequent risk of both psychotic symptoms and schizophrenia-like psychoses (6).

The aim in this study is not to produce a definitive cost-benefit verdict on cannabis licensing and regulation, because a definitive analysis is simply not possible, given the limited evidence that is available. The main purpose of this review is *Cannabis sativa* medicinal and recreational uses, its eventual benefits and marketing regulation. A brief historical perspective concerning cannabis use, plant taxonomy, morphology and some cultivation practices will be mentioned. Some benefits associated with cannabis chemical composition and how they can impact on some known pathologies as well as adverse health effects of non-medical cannabis use will also be addressed. In addition, the positive and negative aspects of this plant's use and its legalization in some countries including Portugal will be tackled.

It is important to mention that the author is not committed to any ideological position in relation to illicit drugs, nor did start with any specific view about the desirability of a licensed and regulated cannabis market.

Materials and Methods

A bibliographic review of the topic was carried out in online academic journals, news websites, books and documentaries, gathering and comparing the different data found in the consultation sources. This narrative review of the literature was accomplished through database search, being this data collection performed between the 16th of March and the 13th of October on the following platforms: NCBI, ScienceOpen, Público, Sapo 24, RTP Notícias, DrugBank, Elsevier and other websites. The search was made by looking for keywords such as: Cannabis *sativa*, cannabinoids, medicinal cannabis and recreational cannabis.

Brief History and Geographical Distribution

Cannabis sativa L. is believed to be one of the oldest crops cultivated by humans (1). The plant has been consumed for food and animal feeds, fibre, paper, oil production, weaving cloth as well as aromatic resin for recreational and medicinal purposes, since Neolithic times. Nowadays its use has changed greatly, being best known for its human mental and physical altering effects (2) (3).

Cannabis first appearance as a multipurpose plant, was believed to be in central Asia about 5000 B.C. (7). However, the first record of the hemp plant culture for fibre and/or achenes fruit (8), was by the prehistoric Scythians (9).
There is strong archaeological evidence of the widespread use of hemp in China as an economic crop by around 4500 B.C., being the oldest written record of the use of hemp a Chinese herbal from the third millennium B.C. In addition to that, ancient literature of China describe methods of cannabis cultivation, where it has been utilized continuously for at least six thousand years (8). Dating back to about 1000 B.C., hemp had probably migrated with nomads and traders, through the Silk Road, being spread over India, Middle East, Africa and Europe. In Persia and Arabia hemp was used as a drug because the term 'hashish', an Arabian word taken from 'hashish al kief', meaning 'dried herb of pleasure'. In Egypt, by around 1000 B.C., the presence of hashish was found in the body tissues of mummies. Plant cultivation spread from India to Arabia, eastern Africa, southern Africa, and South-East Asia (9) (Fig. 1). Currently cannabis has become a world widespread plant and, paradoxically, it is mostly an illicit cultivation herb (4). Therefore information concerning cannabis dissemination and cultivation is not completely reliable (10)

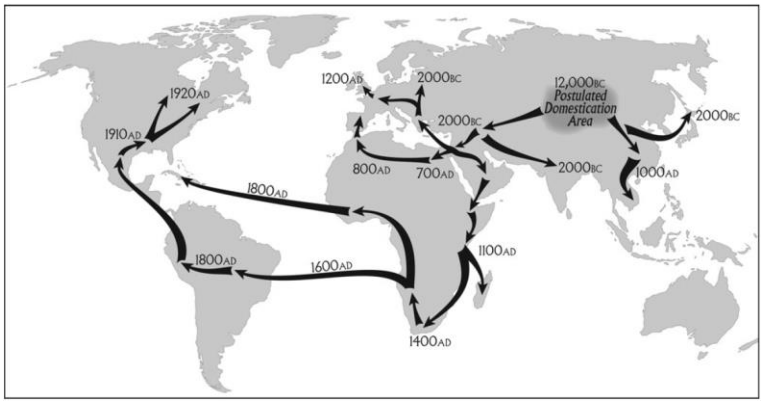

FIGURE 1 - Historical diffusion of *Cannabis sativa* (11)

Taxonomy

The taxonomy of cannabis has generated controversy and continues to evolve as breeding and selection over the centuries originated morphological dissimilarities, without reflecting a meaningful genetic variety (7).

In his original 1753 classification, Carl Linnaeus identified just one species and name it *Cannabis sativa* (14). The genus name *Cannabis* means "cane-like," while the species epithet *sativa* means "sown", meaning that the plant is propagated from seed, and not from perennial roots. According to the modern system of classification, *C. sativa* belongs to Eukaryota Domain, Plantae Kingdom, Spermatophyta Phylum, Angiospermae Subphylum, Dicotyledonae Class and Family Cannabaceae (14). Some authors still consider only one taxon, *C. sativa*,

while others also mentioned *C. indica* and *C. ruderalis* which are also referred as varieties or as subspecies of *C. sativa* (7).

On one hand, *sativa*-type plants, tall and with narrow leaves, are widely believed to produce marijuana with a stimulating and cerebral psychoactive effect, which Δ^9-tetrahydrocannabinol (THC) content is higher. On the other hand, *indica*-type plants, short and with wide leaves, are reported to produce marijuana that is sedative and relaxing, because it has higher cannabidiol (CBD) content (12) (13).

It is also important to refer that the natural selection verified by the introduction in different climates and the human selection to obtain plants with certain characteristics, resulted in a great diversity of forms of growth and of chemical compositions. Taking all into consideration, according to a few authors in (12), "We conclude that the genetic identity of a marijuana strain cannot be reliably inferred by its name or by its reported ancestry".

Morphology

C. sativa is an annual dioeciously flowering plant, with male and female flowers found on separate plants (Fig. 2) (7). The roots are adventitious, with branched taproot, generally 30–60 cm deep, up to 2.5 m in loose soils, very near to the surface, and more branched in wet soils. The stems are erect, usually angular, furrowed, branched, with woody interior, sometimes hollow in the internodes, and vary from 1 to 6 m in height. The branching is either opposite or alternate. Its leaves are green and palmate, having seven lobes. The leaf arrangement is either opposite, alternate or spiral. The leaflets are 6–11 cm (length) and 2–15 mm (width). Leaf margins are coarsely serrated. The adaxial and abaxial surfaces are green, with scattered, resinous trichomes. However, it is important to mention that the size and shape of the leaflets differs markedly, according to genetic origin, speaking even in subspecies of narrow leaf and broad leaf that also correspond to different cannabinoids composition, as mentioned before (12). Inflorescences consist of numerous flower heads that can be found on long, leafy stems from each leaf axil. The staminate (male flower) consists of five pale-green, hairy sepals about 2.5–4 mm long, and five pendulous stamens, with slender filaments and stamen. The pistillate (female flowers) are almost sessile and are in pairs. The fruit is an achene, contains a single seed with a hard shell tightly covered by the thin wall of the ovary, and it is ellipsoid, slightly compressed, smooth, about 2–5 mm long, generally brownish and mottled (7).

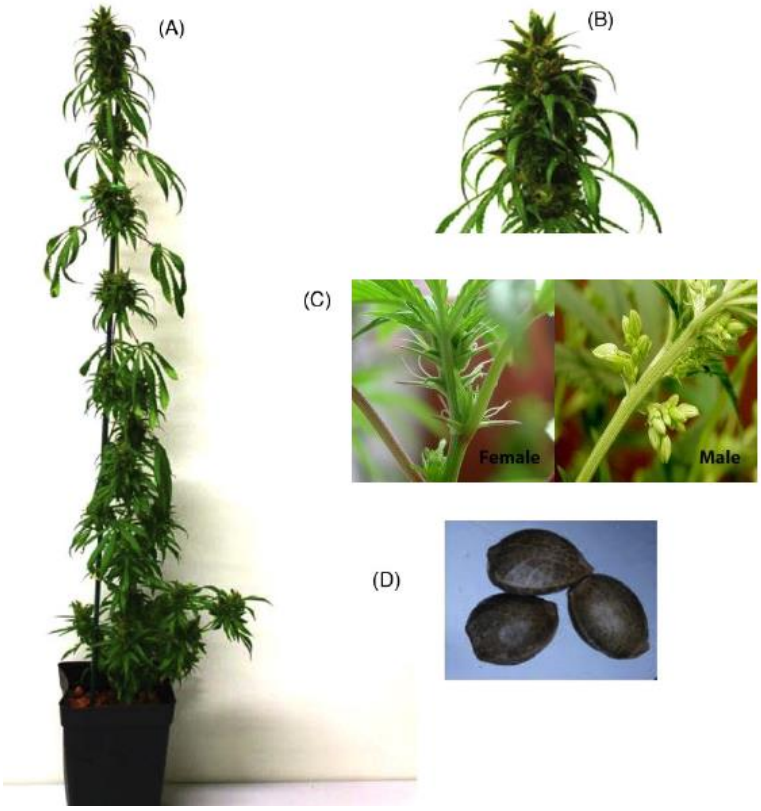

FIGURE 2. *Cannabis sativa* plant: (A) female plant; (B) female inflorescence; (C) detail of female and male flowers; (D) mature seeds (7) (14).

Cultivation Practices

Cannabis cultivation is prohibited in most countries, except by permission for research purposes and pharmaceutical uses (7). *C. sativa* is a demanding culture, it grows well in nutrient rich, well drained, well structured, silty loam soil with high organic matter, being the optimal temperature growth between 21ºC-26ºC. It has a growth period of 2-10 months, which is dependent on the latitude.

In fact the culture of cannabis may have different objectives, that is, a major fibre content or a major cannabinoids content. Since the 1940s, fibre hemp breeders have been reducing the THC content (15). Conversely, breeders of drug cannabis have been increasing the THC content (9). Nowadays, fibre hemp is cultivated in warm humid climates around the world, being China the largest producer of cannabis with focus on fibre-type (16).

In the early 1970s, a handful of North American illicit marijuana cultivators began to grow sinsemilla (without seed) marijuana that within a few years became the predominant style of North American and European marijuana production. The sinsemilla effect is achieved by eliminating male plants from the fields, leaving only the unfertilized and therefore seedless female plants to mature for later flower and/or resin harvest. In lieu of setting seed in the earliest flowers, the female plants continue to produce additional flowers covered by resin trichomes, which increases the percentage of psychoactive and medically valuable THC or other cannabinoids in these flowers (17), as “Dried sinsemilla inflorescences can contain more than 20% THC and/or CBD by weight.” (18). Sinsemilla breeders have selected primarily for

stronger potency (higher THC content) as well as complex aromas and flavours, which are all traits related to terpeno-phenolic secondary product metabolism in the glandular trichomes (18).

Outdoor Cultivation

Cannabis plants can be propagated from seeds, and their life cycle is completed within 4–6 months, depending on the time of the plantation and the variety. Plants can reach up to 5 m (16 ft.) in height (2). Hermaphroditic varieties of this plant have been bred for industrial hemp production, as this allows more uniform crops (23).

Later in summer, the reproductive phase of cannabis begins when the plant is exposed to short day time lengths (less light per day than darkness) of 12–14h or less, depending on its latitude and genetic origin. The produced seeds after flowering have combinations of traits from two parents, as a result of cross fertilization. This method is mostly used for the cultivation of cannabis for hemp fibre, or cannabis seed with less than 0.2% THC. Innovative classical breeding techniques have also been used to improve recreational drug forms of cannabis, resulting in many cannabinoid-rich cultivars.

Indoor Cultivation

The biosynthesis of cannabinoid compounds is unique to cannabis, and cultivars with specific chemical profiles are being developed for diverse industrial and pharmaceutical uses. The complete growth cycle, quality and quantity of biomass can be regulated under controlled environmental conditions (6–8 weeks). For controlling flowering and plant biomass, indoor cannabis crop cultivation needs artificial light and compressed CO_2 gas for photosynthesis (2) and can have an effective system to deliver nutrients and oxygen, which support the plants 'growth. However, there is a few different techniques that have been proposed for the indoor culture of cannabis, for example, the standing aerated technique, the nutrient film technique, and the aeroponics technique. In hydroponic growing, the nutrient solution is best at a pH within a certain range (5.5–6.5) for maximum uptake and good plant growth (25). Here, selective vegetative female plants are used for making clones. Later, all clones are kept under standard environmental conditions (light, temperature, relative humidity, and CO_2 concentration) in a growing room for vegetation (18 h/day photoperiod) and for flowering (12 h/day photoperiod) (2).

This method of breeding is as well used for increasing resin potency, avoiding unwanted male plants (24). Female cannabis flowers produce a preponderance of resin glandular trichomes that secrete a cannabinoid and terpene-rich essential oil. Selection for high production of resin and essential oil is the driving force in modern-day drug cannabis breeding, to the virtual exclusion of other agronomically valuable traits (18). Hemp cultivars are maintained as select elite populations, which ensures inbreeding to preserve these favourable traits (18).

Chemical Composition

Due to the vast number of its constituents and their possible interaction with one another, we can say that cannabis is very complex genus in its chemistry. The total number of natural compounds identified in *C. sativa* until 1980 was 423 but in 1995 they were already 483 (19).

These compounds belong to almost all of the chemical classes:[classes number known] nitrogenous compounds [27], amino acids [18], proteins [3], enzymes [6], glycoproteins [2], sugars and related compounds [34], hydrocarbons [50], simple alcohols [7], simple aldehydes [12], simple ketones [13], simple acids [20], fatty acids [23], simple esters [12], lactones [1], steroids [11], terpenes [120], non-cannabinoid phenols [25], flavonoids [23], vitamins [1] and pigments [2] (19).

Cannabis plants produce many compounds with biological and pharmacological activities (17). So that over the last few years there have been an active debate regarding the medicinal aspects concerning the use of cannabis, attributed to many of these compounds (6) (7). In USA, currently cannabis products are classified as Schedule I drugs under the Drug Enforcement Administration (DEA) Controlled Substances act, which means that the drug is only available for human use as a research drug only (19). According to Farag and Kayser (20), the plant contains a number of medicinal important chemical groups of compounds such as: cannabinoids (21), terpenoids (22), flavonoids (23), alkaloids (24) and others (20). Cannabinoids are a unique class of terpene-phenolic compounds only found in *Cannabis* species, accumulated mainly in the trichomes (Fig. 3) (25). It is important to mention that the female plants continue to produce additional flowers covered by resin glands, when they are not fertilized, which increases the percentage of psychoactive and medically valuable THC (17).

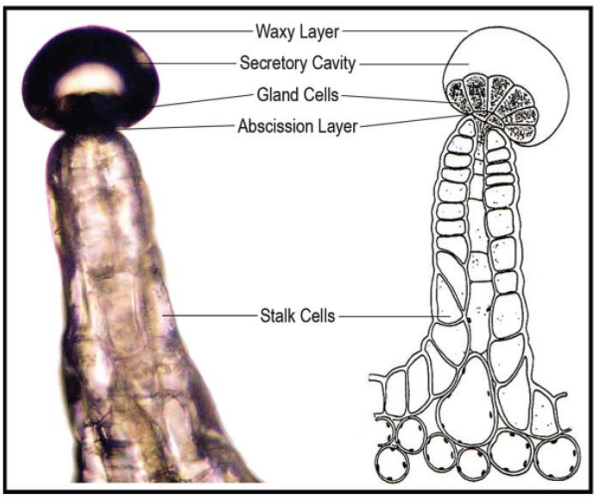

FIGURE 3 *Cannabis sativa* trichome (17)

Cannabinoids are a typical C_{21} group of compounds present in *C.* sativa (19). More than 80 cannabinoids have been isolated from cannabis (19). The main psychoactive compound, with well-known medicinal effects (26), is THC, being its chemical structure identified in 1964 (17) (Fig 4)

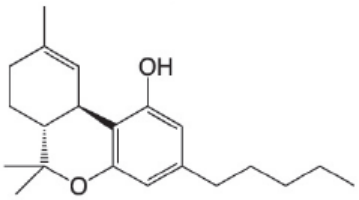

FIGURE 4 Δ^9-tetrahydrocannabinol (27)

Cannabidiol, a non-psychoactive cannabinoid (28), isolated in 1940 (19), represents the most promising one from the pharmaceutical point of view, due to its high anti-oxidant, anti-inflammatory activity, anticonvulsant, anxiolytic, neuroprotective, and antibiotic properties (29) (Fig 5).

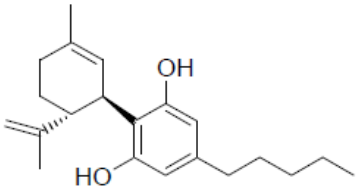

FIGURE 5 Cannabidiol (29)

Twenty-three flavonoids have been identified in cannabis (17), which are associated with a broad spectrum of health-promoting effects (30). Flavonoids, may also modulate the pharmacokinetics of some cannabinoids, by inhibiting of hepatic P450 enzymes (29).

As regards the other compounds present in hemp, terpenes are responsible for the characteristic aroma of the plant. In relation to monoterpenes, myrcene is known to possess anti-inflammatory, analgesic, and anxiolytic properties (29). As for sesquiterpenes, caryophyllene was found to be an anti-inflammatory agent and to exert a gastric cytoprotector activity (29). It is important to mention that there is synergistic action between cannabinoids and terpenes. As an example, terpenes are able to increase blood-brain barrier permeability and they can also interact with neurotransmitter receptors, thus contributing to cannabinoid-mediated analgesic and psychotic effects (29).

It is undoubtedly needed a detailed chemical characterisation of the plant material in order to guarantee a better reproducibility of biological assays and to monitor its composition (29).

There are morphologically identical plants that are chemically different, called as chemotypes. This is important, as the selection of a particular phenotype does not mean the selection of a precise chemical composition. In *C. sativa*, environmental temperature growth conditions influence the cannabinoid content. Cold temperatures make some plants produce higher quantities of THC, for example (31). Therefore it is important to know the chemical characterisation of the plant, not only for ensure the efficacy and safety of hemp-based products to be used in the pharmaceutical and nutraceutical fields, but also to ensure quality control (29).

It is important to mention that according to monographies, cannabis extract for medicinal purpose is "the extract produced and adjusted from the whole or fragmented, flowering, dried shoot tips of the female plants of *Cannabis sativa* L.” (32)

Pharmacology

In general there are two types of cannabinoid receptors, CB_1 and CB_2 (33). Both differ in signalling mechanisms, tissue distribution, and sensitivity to certain agonists and antagonists that show marked selectivity for one or the other receptor type (33). THC is an agonist to both types and CBD only displays CB_1 antagonism (34)(35). The cannabinoid receptors are distributed in the central nervous system in areas that regulate appetite, memory, fear, hypothalamus, and posture such as the hippocampus, basal ganglia, basolateral amygdala, motor responses, cerebellum (27) and in many peripheral tissues including spleen, leukocytes; gastrointestinal, urinary and reproductive tracts; endocrine glands, arteries and heart (33).

The identification of cannabinoid receptors is followed by the detection of endogenous ligands for these receptors, called endocannabinoids, that together with cannabinoid receptors and enzymes responsible for the synthesis and degradation of endocannabinoids (36) constitute the cannabinoid system (33). Perturbations of the cannabinoid system are involved in several psychiatric disorders, including schizophrenia (36). However, the mode of action of cannabinoid system is not fully understood and several mechanisms have been proposed (33).

On one hand, elevated levels of endocannabinoid have been demonstrated in a pain circuit of the brain (periaqueductal gray) following painful stimuli. On the other hand, an increase of cannabinoid receptors following nerve damage was demonstrated in animal models intestinal inflammation and chronic neuropathic pain (33), which may increase the potency of cannabinoid agonists used for the treatment of these conditions (33).

Both CB_1 and CB_2 signal through the transducing G proteins and their activation by THC or other agonists causes: the inhibition of adenylyl cyclase activity, the closing of voltage-gated calcium channels, the opening of inwardly rectifying potassium channels, and the stimulation of mitogen-activated protein kinases such as extracellular signal (27).

Cannabinoids interact with a multitude of neurotransmitters and neuromodulators among them: acetylcholine, prostaglandins, histamine, γ-aminobutyric acid (GABA), serotonin, glutamate, dopamine, norepinephrine, and opioid peptides. Several pharmacological effects can be explained based on such interactions (33):

- Tachycardia and hyposalivation with dry mouth are mediated by effects of THC on release and turn-over of acetylcholine;
- Cannabinoid agonists inhibited the activation of serotonin receptors, what may explain antiemetic properties of cannabinoids;
- Therapeutic effects in movement/spastic disorders could be ascribed due to interactions with GABAergic, glutamergic and dopaminergic transmitters systems.

The cannabinoid system has also a role in appetite and eating, bone formation, cancer, digestive tract, eye, hormonal system and fertility and immune system (33)(35). It has been implicated in various aspects of addiction, such as drug-seeking and relapse (37).

One important physiological role of endocannabinoids is neuroprotection, so that THC was neuroprotective in rats given the toxic agent ouabain. Clinical studies under way investigating the therapeutic potential of a non-psychotropic derivative of THC in acute conditions (head trauma) showed first positive results (33).

In cannabidiol sedation, anti-epileptic, anti-dystonic, anti-emetic and anti-inflammatory effects have been observed. It also reduces intraocular pressure, is neuroprotective, and antagonizes the psychotropic and several other effects of THC (33). It can also enhance adenosine receptor signalling by inhibiting adenosine inactivation, suggesting a potential therapeutic role in pain and inflammation (27). Pre-treatment with CBD is associated with lower THC-induced psychotomimetic effects, paranoia and verbal memory impairments (34) because the antioxidant and anti-inflammatory properties of CBD may explain its potential neuroprotective actions (27). Furthermore, during processing of fearful faces, THC resulted in increased psychotic symptoms and skin conductance responses, whereas CBD led to a reduction in anxiety and a decrease in skin conductance response (34). Also, THC and CBD had opposite effects on blood oxygen–level dependent responses in tasks of verbal recall, response inhibition, processing fearful facial expressions, auditory processing, and visual processing (34).

The most common acute adverse effects of cannabis consumption are anxiety, panic reactions, and psychotic symptoms, all of which are most often reported by naive users (38)(39). The acute toxicity of cannabinoids is very low because they do not produce respiratory depression like the opioids (39).

THC can induce tachycardia (by vagal inhibition), and increase cardiac output with increased cardiac labour and oxygen demand (33). It can also produce peripheral vasodilation and orthostatic hypotension (33). Hypotension is mediated by central inhibition of the sympathicus, obviously by activation of CB_1 receptors since this effect can also be prevented by a CB_1 antagonist (33).

Tolerance can mainly be attributed to pharmacodynamic changes, presumably based on receptor downregulation and/or receptor desensitisation (33). One study showed that selective down-regulation of CB_1 receptors in several cortical brain regions in long-term marijuana smokers was correlated with years of cannabis smoking and was reversible after 4 weeks of abstinence (2).

Mechanisms of action of cannabinoids are complex and there is still much to learn about the physiological role of the natural ligands to the CB receptors and about long-term effects of cannabis use.

Medicinal uses

‘Medicinal cannabis’ means ‘relating to or having the properties of a medicine, a curative, a remedial’. In this way, cannabis should be regarded as ‘medicinal cannabis’ when it is used for a medicinal objective. (40).

Researchers at the University of Sydney have identified what they refer to as the ‘big 10’ non-psychoactive and non-addictive cannabinoids that show the most promising therapeutic potential. They are:

- cannabidiol (CBD) and its acid form (CBDA)
- cannabidivarin (CBDV)
- the acid form of THC (THCA)
- tetrahydrocannabivarin (THCV) and its acid form (THCVA)

- cannabigerol (CBG) and its acid form (CBGA)
- cannabinol (CBN)
- cannabichromene (CBC) (40)

Medicinal cannabinoids can be administered in various ways: orally, topically, sublingually smoked, inhaled, mixed with food, or into tea. They can also be taken in herbal form, extracted naturally from the plant, grew by isomerisation of cannabidiol or manufactured synthetically (41). Prescribed cannabinoids include Dronabinol capsules (synthetic THC), Nabilone capsules (a synthetic cannabinoid similar to THC), and the oromucosal spray Nabiximols (41).

The categories of herbal products made available for medicinal purposes include:

- the dried flowering tops of the cannabis female plants taken through being smoked, vaporised or infused in tea;
- extracts of cannabis, containing concentrated extracts of cannabinoids, taken orally, topically or by vaporisation;
- raw, undried cannabis leaves, consumed as a food;
- cannabis resin, collected and compressed from the flowering tops of the female plants;
- infused cannabis products, such as alcohol-based tinctures, edible oils infused with cannabis and products made from these, and suppositories (40).

A study published in the British Journal of Pharmacology suggested that terpenes can inhibit the psychoactive effects of THC, increasing the potential of cannabis-based medicinal extracts to treat pain, inflammation, depression, anxiety, addiction, epilepsy, cancer, fungal and bacterial infections, including methicillin-resistant *Staphylococcus aureus* (42).

The report also indicates that there is some evidence for the benefit of using marijuana to decrease intraocular pressure in the treatment of glaucoma. Nonetheless, the report stresses the importance of focusing research efforts on the therapeutic potential of synthetic or pharmaceutically pure cannabinoids (2).

Neurological disorders

There is evidence that CBD could potentially be exploited in the treatment and symptom relief of various neurological disorders such as seizures and epilepsy, psychosis, anxiety, movement disorders and multiple sclerosis (21). THC capsules may be associated with a significant improvement in tic severity in patients with Tourette syndrome (36). Given the broad effects of CBD as a neuroprotective, anti-inflammatory, immune-modulator agent and furthermore considering its lack of psychoactive activity, it represents a possibility for cannabinoids in clinical use (43).

<u>Multiple sclerosis</u>

Multiple sclerosis is a chronic neuroinflammatory disease with unknown aetiology and variable clinical evolution. It is an immune mediated disorder of the central nervous system characterized by the destruction of myelin sheath that surrounds the axons (43).

According to Penny F. Whiting (41), there was moderate-quality evidence to support the use of cannabinoids for the treatment of chronic pain and spasticity, however, cannabinoids were associated with an increased risk of short-term adverse effects.

Combinations of THC and CBD have shown efficacy in the treatment of spasticity associated with multiple sclerosis. For example, Sativex an oromucosal spray of a formulated extract of *C. sativa* that contains the principal cannabinoids THC and CBD in a 1:1 ratio (44). This may be partly related to its analgesic effects, but also to its anti-inflammatory and other properties (1).

Epilepsy

The term "epilepsy" refers to a complex group of neurological disorders, characterized by recurrent epileptic seizures (43). Epilepsy can contribute to low self-esteem, anxiety, depression, impaired memory and attention, lack of independence, and social stigma (45).

Despite continued development of new medications for the treatment of epilepsy, nearly 1 in 3 patients remain drug-resistant (46). Uncontrolled epilepsy is associated with an increased risk of morbidity including neuropsychological impairment, psychiatric, psychosocial difficulties and behavioural disturbances (47).

Cannabis contain more than 100 terpenoid compounds of which THC, CBD, CBN, CBDV and THCV showed anticonvulsant properties in variety of animal models. (48).

The use of enriched CBD oil in the treatment for intractable paediatric epilepsy patients is becoming increasingly popular (49), since CBD showed anticonvulsant effects on both in vitro and in vivo experiments (43). The absence of psychoactive action of CBD and its potential efficacy as an anticonvulsant has made it a very interesting molecule as a new potential therapeutic tool for patients with medically refractory epilepsy (43) (46).

Psychotic disorders

Cannabinoids have also emerged as a new class of drugs with potential effects over a broad range of neurodegenerative and psychiatric disorders (50). Studies have been undertaken on the use of various cannabis products in treating obsessive-compulsive disorder, schizophrenia and Tourette's syndrome, once cannabinoids are thought to have possible antipsychotic effect. However, much of this research is still quite preliminary or has not yet yielded clear results (1).

Alzheimer disease

CBD protected cells from the damaging action of Aβ peptide (neurotoxic aggregates), by a combination of its antioxidant, anti-apoptotic and anti-inflammatory properties (43).

Parkinson disease

CBD displays anti-inflammatory and antioxidant actions, and both inflammation and oxidative stress are linked to the pathogenesis of various movement disorders, such as Parkinson disease or Huntington's disease (51).

So far, no treatment has been shown to cure Parkinson and none has been approved to slow or reverse the neurodegenerative process of the disease (43). However, there is a lot of evidence of a role of CBD in neuroprotection and neuropsychiatric disorders (43).

Only few trials were conducted on Parkinson's disease patients. Zuardi (51), reported a study on 6 patients, treated with levodopa. The subjects received treatment with CBD for 4 weeks in addition to their usual therapy and significant improvements in total scores of Brief Psychiatric Rating Scale and the Parkinson Psychosis Questionnaire were observed. Moreover, the treatment also significantly decreased psychotic symptoms (43), without worsening the motor function or inducing adverse effects (51). Treatment with CBD for 6 weeks improves undoubtedly patients quality of life (51).

Huntington's disease

Huntington's disease is an inherited fatal progressive neurodegenerative disease that causes motor dysfunctions, emotional problems and cognitive loss (43)(51). At present, cannabinoids have been studied to alleviate hyperkinetic symptoms, given their inhibitory effects on movement, and due to their anti-inflammatory, neuroprotective and neurodegenerative properties (43).

In a study CBD and other three cannabinoid compounds tested (Δ^8-THC, Δ^9-THC, and CBN) show 51–84% protection against the huntingtin-induced cell death by antioxidant mechanisms (51).

It is noteworthy that in some cases, CBD per se does not seem to be beneficial. However, when CBD is administered with Δ^9-THC in a 1:1 ratio, therapeutic effects are observed. Therefore, it is also important to evaluate the interactions between CBD and THC as well as the adverse effects of this mixture (51).

Relief on secondary effects of carcinogenic diseases and on chronic pain

Cancer diseases

Patients with different types of cancer diseases are using cannabis to manage a multitude of secondary effects, such as pain, anxiety, sleep, depression, nausea, vomiting, appetite loss, and to improve quality of life (42).

The authoritative report by the Institute of Medicine, Marijuana and Medicine, acknowledges the potential benefits of smoking marijuana in combating chemotherapy-induced nausea and vomiting, severe pain, and some forms of spasticity (40). In 2016, The American Society of Clinical Oncology published guidelines to help cancer survivors manage chronic pain and these recommendations included the use of cannabis and cannabinoid-based medicines (42). When taken medicinal cannabis, it is possible to experience pain relief and comfort specially by patients with terminal cancer (40).

Furthermore, the combination of THC and CBD may provide the best utility for pain management, which is good for the treatment of severe neuropathic-related cancer pain (9).

In cancer treatment, cannabinoids, such as Dronabinol and Nabilone are mainly used in association with chemotherapy in order to decrease its side effects, although their use is still limited due to their psychoactive side effects (52).

Chronic pain

Cannabinoids and terpenes are effective in pain relief, so that cannabis can be a helpful analgesic adjuvant in patients with cancer, which can either reduce or eliminate opioid requirements (42).

The National Academy of Sciences, in their 2017 report titled The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research, stated that "There is conclusive or substantial evidence that cannabis or cannabinoids are effective for the treatment for chronic pain in adults" (42).

A large number of the people who attended the public consultations had used medicinal cannabis for chronic pain (40), since the endocannabinoid system is a modulator of nociception (44). Removing the barriers to access of medical cannabis for clinical care will provide options in managing pain while helping patients regain function (44).

Weight gain in HIV

The authoritative report by the Institute of Medicine, Marijuana and Medicine, acknowledges the potential benefits of smoking marijuana in stimulating appetite, particularly in patients with the acquired immunodeficiency syndrome (AIDS) and the related wasting syndrome (1). Trials of oral THC (Nabilone or Dronabinol), have shown it has efficacy for appetite stimulation and weight gain among patients with HIV, advanced cancer and anorexia (1).

Anxiety and insomnia

Consumption of medical cannabis flower is associated with significant improvements in perceived insomnia with differential effectiveness and side effect profiles, depending on the product characteristics (53). Evidence exists for the anxiogenic effect of THC and the anxiolytic effect of CBD (54). Higher CBD levels are associated with greater symptom relief even after controlling for other characteristics of the flower consumed (53).

Cannabis indica strains are horticulturally bred to enhance sedative effects and are recommended for symptoms of anxiety and insomnia (44), since products made with *C. sativa* are associated with less symptom relief and more negative side effects than products made from *C. indica* or hybrid plant subtypes (53).

CBD has unique pharmacologic, physiologic, and behavioural effects with suggestions of salutary effects on brain substrates subserving anxiety, mood and sleep complaints (4).

Carcinogenic diseases

A lot of studies have demonstrated that cannabinoids exert antiproliferative and anti-invasive actions in a large number of cancer types (43). Several reports showed that CBD exhibits anti-proliferative, pro-apoptotic effects and inhibits cancer cell migration, adhesion and invasion (43).

The endocannabinoid system seems to play a tumour suppressing role on colon carcinoma in a genetic modified mouse model, since cannabinoids might interfere with cancer biology, acting on CB_1 and CB_2 receptors in a wide range of cancer types (52). It has also been highlighted a beneficial effect of combined treatment of CBD with THC that enhances inhibitory effect on cell growth in vitro and in vivo models (43).

Post-traumatic stress disorder (PTSD)

Considerable attention has been directed at Post-traumatic Stress Disorder (54).

PTSD is a chronic psychiatric condition that may develop after experiencing a potentially traumatic event. The disorder manifests itself at different levels, through symptoms such as sleep disturbances, mood (depression, anxiety), changes in cognition (repeated recall of the event), emotion (psychological instability), and reduced social skills (55).

Preclinical studies in different rodent behavioural models have shown that CBD can, both facilitate the extinction of aversive memories and block their reconsolidation, possibly through potentiation of the endocannabinoid system (55). CBD also shows an action profile with fewer side effects than the pharmacological therapy currently used to treat this type of disorder (55).

Possible therapeutic targets for CBD or similar agents would include: neuropathic pain (causalgia, complex regional pain syndrome, migraine), burns, irritable bladder, interstitial cystitis, prostatitis, chronic pelvic pain, fibromyalgia, inflammatory bowel disease, irritable bowel syndrome, pancreatic pain, and various dermatological pruritic conditions, since it does not cause pain acutely (35). On table 1 there is an overview of CBD pharmacological effects.

TABLE 1

Overview of CBD pharmacological effects (43)

Disease	Effects
Alzheimer's disease	Anti-inflammatory, antioxidant, antiapoptotic in in vitro and in vivo models of Aβ-evoked neuroinflammatory and neurodegenerative responses.
Parkinson's disease	Attenuation of the dopaminergic impairment in vivo; neuroprotection; improvement of psychiatric rating and reduction of agitation, nightmare and aggressive behaviour in patients.
Multiple sclerosis	Improved signs of EAE in mice, anti-inflammatory and immunomodulatory properties
Epilepsy	Anticonvulsant in vitro and in vivo; reduced seizures frequency in children and adults with treatment-resistant epilepsy.
Huntington's disease	Neuroprotective and antioxidant in mice transgenic models; no significant clinically important differences in patients.
Hypoxia-ischemia injury	Short term neuroprotective effects; inhibition of excitotoxicity, oxidative stress and inflammation in vitro and in rodent models.
Pain	Analgesic effect in patients with neuropathic pain resistant to other treatments. Attenuation of the behavioural and glial changes in animal models of schizophrenia; anti-psychotic properties on ketamine-induced symptoms
Anxiety	Reduction of muscular tension, restlessness, fatigue, problems in concentration, improvement of social interactions in rodent models of anxiety and stress; reduced social anxiety in patients.
Depression	Anti-depressant effect in genetic rodent model of depression.
Cancer	Antiproliferative and anti-invasive actions in a large range of cancer types; induction of autophagy-mediated cancer cell death; chemopreventive effects.
Nausea	Suppression of nausea and conditioned gaping in rat
Inflammatory diseases	Anti-inflammatory properties in several in vitro and in vivo models; inhibition of inflammatory cytokines and pathways.
Rheumatoid arthritis	Inhibition of TNF-α in an animal model
Infection	Activity against methicillin-resistant Staphylococcus aureus
Inflammatory bowel and Chron's diseases	Inhibition of macrophage recruitment and TNF-α secretion in vivo and ex vivo; reduction in disease activity index in Chron's patients.
Cardiovascular diseases	Reduced infarct size through antioxidant and anti-inflammatory properties in vitro and in vivo.
Diabetic complications	Attenuation of fibrosis and myocardial dysfunction

Adverse health effects of non-medical cannabis use

The rising use of cannabis has heightened community concern about its impact on the health and psychological development of young people because of observations that regular cannabis users are more likely to use other illicit drugs, perform poorly in schools, and report psychotic symptoms, depression and poorer mental health than their peers (39), since cannabinoids produce acute transient: dose-related deficits in memory, abstract ability, executive function, decision making and attention (6).

The popular notion seems to be that marijuana is a harmless pleasure, access to which should not be regulated or considered illegal (2). This leads to recreational use: in social settings to increase sociability and produce euphoric and intoxicating effects (38). People who are more susceptible to drug-taking behaviour are simply more likely to start with marijuana because of its accessibility and that their subsequent social interactions with other drug users would increase the probability that they would try other drugs (2).

The most common route of administration is inhalation and the evidence clearly indicate that long-term marijuana use can lead to addiction (2). The amount of THC delivered to the lungs varies between 20% and 70%, and 5% to 24% reaches the brain (38). No reliable information exists about the concentration of THC and other cannabinoids in commonly used cannabis products (38). The effects of cannabis depend on the dose received, user's previous experience with this drug, the mode of administration and the setting (38). The dose of THC that kills rodents is very high and the estimated fatal human dose is between 15g and 70g (38).

The most common adverse unpleasant effects of occasional cannabis use are anxiety and panic reactions (39). The most probable adverse effects include a dependence syndrome, increased risk of motor vehicle crashes, impaired respiratory function, cardiovascular disease, adverse effects of regular use on adolescent psychosocial development and mental health (38).

The THC-induced negative effects, similar to the negative symptoms of schizophrenia, although studied less frequently than positive symptoms, include blunted affect, emotional withdrawal, psychomotor retardation, lack of spontaneity and reduced rapport (34).

Chronic Cannabis use

Chronic cannabis use has usually been defined as regular use, especially daily or near daily, over periods of years (38)(39). A major problem in interpreting epidemiological studies of chronic cannabis use is that it is also correlated with other drug use, which is known to adversely affect health (e.g. alcohol and tobacco use) (39). The chronic health effects are less certain because the evidence is from observational studies that often have limited ability to adequately control for major sources of confounding or to rule out reverse causation (39).

Regular users have a higher risk of chronic bronchitis and impaired respiratory function, psychotic symptoms and disorders, most probably if they have a history of psychotic symptoms or a family history of these disorders (38).

Animals and human beings develop tolerance to many of the effects of THC (38)(39). Withdrawal symptoms include anxiety, insomnia, appetite disturbance, and depression. (38). These symptoms appear within 24 h of cessation and are most pronounced for the first 10 days (39).

Larger cohort and better designed case–control studies are needed to clarify whether any such risks from chronic cannabis smoking exist (38).

Adolescent exposure and brain damages

Studies in animals have shown that prenatal or adolescent exposure to THC can recalibrate the sensitivity of the reward system to other drugs and that prenatal exposure interferes with cytoskeletal dynamics, which are critical for the establishment of axonal connections between neurons (2).

In addition to that, longitudinal studies have shown a relation between cannabis use in young individuals before the age of 15 years and early school leaving that has persisted after adjustment for confounders (38). In addition to that, the earlier the age at which a young person uses cannabis, the more likely they are to use heroin and cocaine (38).

As compared with unexposed controls, adults who smoked marijuana regularly during adolescence have impaired neural connectivity (fewer fibres) in some specific brain regions. These include the precuneus, a key node that is involved in functions that require a high degree of integration (e.g., alertness and self-conscious awareness), and the fimbria, an area of the hippocampus that is important in learning and memory (2).

Three explanations have been given for these patterns of drug involvement: cannabis users have more opportunities to use other illicit drugs because cannabis is supplied by the same black market; those who are early cannabis users are more likely to use other illicit drugs for reasons that are unrelated to their cannabis use; and pharmacological effects of cannabis increase the propensity to use other illicit drugs (38).

Cannabis, THC and synthetic cannabinoids produce acute, transient, and dose-related cognitive impairments in executive function, abstract ability, and decision making (34). The most robust effects are on verbal learning, short-term memory, working memory, and attention, consistent with effects in rodents and nonhuman primates (34). In addition, imaging studies in people who use cannabis have revealed decreased activity in prefrontal regions and smaller amygdala and hippocampal volumes (2)(6). Thus, certain brain regions may be more vulnerable than others to the long-term effects of marijuana (2).

More functional brain imaging studies on larger samples of long-term users are needed to see if cognitive impairments in long-term users are correlated with structural changes in brain areas implicated in memory and emotion (38).

Psychosis

Converging lines of preclinical, epidemiologic, and experimental evidence support an association between cannabinoid agonists psychotic symptoms and schizophrenia-like psychoses (34)(6), however, establishing causality from observational designs can be problematic and difficult (56). On one hand, experimental studies in healthy humans show that cannabis and its active ingredient THC, can produce transient, dose-dependent, psychotic symptoms, as well as an array of psychosis-relevant behavioural, cognitive and psychophysiological effects (6). On the other hand, the psychotogenic effects of THC can be ameliorated by CBD. Psychotic symptoms include disorganized thinking and speech, delusions, and hallucinations (6).

A case-controlled study showed that people using high-potency cannabis on a daily basis were five times more likely than non-users to suffer from a psychotic disorder (6). The results from longitudinal studies show a consistent pattern of association between cannabis and psychosis, which could be indicative of a causal relationship. However, there are a number of reasons why the studies might have overestimated or underestimated the association between cannabis and psychotic outcomes, such as bias, confounding, reverse causation, misclassification bias and attrition (56).

Cannabis extracts as well as THC alone produce a range of transient symptoms, including suspiciousness, paranoid and grandiose delusions, conceptual disorganization, fragmented thinking, and perceptual alterations measured on standardized rating scales such as the Positive and Negative Syndrome Scale, Clinician Administered Dissociative States Scale, Psychotomimetic States Inventory and Brief Psychiatric Rating Scale (34). It is also involved with other mental health disorders such as: schizophrenia and other psychoses; bipolar disorders, anxiety and depression, but causality has not been established in regular marijuana use (2), suicide and posttraumatic stress disorder (27). Psychoactivities include euphoria, hallucination, and analgesia (57).

However, it is inherently difficult to establish causality in these types of studies, factors other than marijuana use may be directly associated with the risk of mental illness. In addition, other factors could predispose a person to both marijuana use and mental illness. This makes it difficult to confidently attribute the increased risk of mental illness to marijuana use (2).

The best evidence that these associations may be causal comes from longitudinal studies: one of the earliest prospective studies of cannabis use and schizophrenia was a 15-year follow up of 50,465 Swedish conscripts. It found that those who had tried cannabis by age 18 were 2.4 times more likely to be diagnosed with schizophrenia that those who had not (39). The risk increased with the frequency of cannabis use and remained significant after statistical adjustment for confounding variables. Those who had used cannabis 10 or more times by age 18 were 2.3 times more likely to be diagnosed with schizophrenia than those who had not (39). A 3-year longitudinal study of the relationship between self-reported cannabis use and psychosis in a sample of 4848 people in the Netherlands found a dose–response relationship between cannabis use at baseline and psychotic symptoms during the follow up period that persisted after statistically controlling for the effects of other drug use (39).

However, risk of develop schizophrenia could be much greater in those at a higher genetic risk or in those who use particularly potent strains of cannabis so that there is strong body of epidemiologic evidence to support the view that regular or heavy cannabis use increases the risk of developing psychotic disorders that persist beyond the direct effects of exogenous cannabinoids (56). Cannabis increases the risk of psychosis in people with certain genetic or environmental vulnerabilities, though by itself, it is neither a sufficient nor a necessary cause of psychosis (58). However, there is a strong need for more robust epidemiologic studies to determine the likely impact of synthetic cannabinoids on risk of psychotic disorders (56).

The respiratory risks of cannabis smoking

Cannabis smoke contains many of the same carcinogens as does tobacco smoke, with some in higher concentrations than tobacco smoke (38) (39), being inhaled more deeply (3). That is,

when smoking cannabis compared with tobacco, there is a prolonged and deeper inhalation and it is smoked to a shorter butt length and at a higher combustion temperature, while tobacco cigarettes are typically smoked in greater frequency, albeit with shorter puff duration (possibly due to the half-life of nicotine; approximately 2h compared with almost 1 week for cannabinoids) (3).

Marijuana smoking is also associated with inflammation of the large airways, increased airway resistance due to bronchodilation and lung hyperinflation (3). These associations are consistent with the fact that regular marijuana smokers are more likely to report symptoms of chronic bronchitis than are non-smokers. Moreover, studies have suggested that cannabinoids affect macrophage functioning such as suppressing phagocytosis, spreading and bactericidal activity (3).

However, the long-term effect of low levels of cannabis smoking on respiratory function does not appear to be significant (39), being the effects of long-term exposure less clear (2), even though smoking cannabis in the long term is likely to cause increased cough and sputum production, damage to the mucosa and affects immunoregulation such that the smoker is predisposed to lower respiratory tract infections (3).

So, there are good reasons for believing that cannabis can cause cancers of the lung and the aerodigestive tract (39). It is also mutagenic and carcinogenic in the mouse skin test, and chronic cannabis smokers show pathological changes in lung cells that precede the development of lung cancer in tobacco smokers (38). However, the effects of long-term marijuana smoking on the risk of lung cancer are unclear (2).

Accidental injury

In the laboratory, cannabis and THC produce dose related impairment in reaction time, information processing, perceptual–motor coordination, motor performance, attention, and tracking behaviour. These effects can increase the risk of accidents if users drive while intoxicated (38). Recent marijuana smoking and blood THC levels of 2 to 5ng per millilitre are associated with substantial driving impairment (2)

Pregnancy, malformations and growth

High doses of cannabis cause growth retardation and malformations in animals, but epidemiological studies have given scarce evidence for an increased risk of birth defects in women who use cannabis during pregnancy (38). Cannabis use in pregnancy has been most consistently associated with reduced birthweight in large epidemiological studies (38), pregnancy complications for the mother; foetal growth and development; neonatal conditions and later outcomes for the infant (27).

Children born to 655 women in Pittsburgh, between 1990 and 1995, were followed up and poorer performances on memory and verbal skills of the Stanford-Binet intelligence scale in 3-year-old children of cannabis users, were found. By 10 years of age, children born to cannabis users showed increased delinquency and behavioural problems (38).

Cannabis non-medicinal uses

Fibre

The long, strong, mildew-resistant fibre in hemp was traditionally used for rope, sails, tarpaulin, bags and carpets. It can also be used for clothing and other textiles. Hemp is an ideal material for production of paper, fibreboard, composite wood products and it may be mixed with lime to create reinforced concrete. The fibres also serve as a fibreglass substitute, for pressed insulation and moulded panels for the car industry (59).

Hempseed

Approximately one-third of hempseed content is oil, which is used in lighting, lubrication, soaps, detergents and cosmetic creams. The fatty acids are quick drying and so hemp oil is useful for paints, varnishes and printing inks. Hemp oil can also be burned as a fuel (59).

The essential oil (which contains no THC) can be used in cosmetics, perfumes, food additives, and it may be fractionated for pharmaceutical use. The oil has antibacterial, antifungal and pest-repellent properties and is being developed as an organic pesticide (60).

Psychoactive substance

The main reason why most people use cannabis is to experience a so-called "high". It consists in mild euphoria, relaxation, and perceptual alterations, including time distortion and intensification of ordinary experiences such as eating, watching films, listening to music, and engaging in sex (38). When used in a social context, the "high" could be accompanied by increased sociability and talkativeness. These effects typically occur 30 min after consumption and last for 1–2 h (38).

There are two types of drug produced:

1. hashish, which is pure resin scraped from the female flowering tops of the plant, the oil obtained from resin is also a product;
2. marijuana, dried unfertilized inflorescences of female plants, or the dried leaves and flowers of the male and female plants. (59).

Marijuana can be smoked in hand-rolled cigarettes called "joints", smoke oils from the cannabis plant (this is called "dabbing") (61)(62), in pipes, water pipes (sometimes called bongs), in blunts (marijuana rolled in the tobacco-leaf wrapper from a cigar) or through electronic vaporizers ("vape pens"), sometimes with tobacco added (61)(62)(38)(2). Marijuana can also be used to brew tea and, particularly when it is sold or consumed for medicinal purposes, is frequently mixed into foods (edibles) such as brownies, cookies, or candies (62).

Edibles

In China, hempseed is commonly eaten, roasted or raw, it is therefore a valuable food supplement. After the oil has been pressed out of the seed, the remaining seed cake is rich in protein and is suitable for use as a flour or an animal feeding (59).

In a medical context, a cannabis edible is a product containing cannabis that is ingested. Examples include oils, tinctures, and oil-filled capsules. In a recreational context, edibles more commonly refer to cannabis infused food products.

One aspect to remember in this new world of 'edibles' is that the ingestion of THC products causes a longer experience compared to smoking and inhalation (63). The psychoactive effects of THC are felt within minutes after smoking, with peak effects reportedly occurring within 10–15 min. In comparison, it takes 30–90 min after consuming an edible for the effects of THC to be knowledgeable. Peak effects occur over a wide range of 2 to 6 hours and can be delayed if the edible is taken after eating a meal. Lastly the duration of effects after smoking are reportedly 2 hour, while the psychoactive effects experienced after consuming an edible can last up to 8 hours depending on factors such as food and dose (64).

Cannabinoid extracts have been added in everyday commodities such as teas or coffees, pizza, lollypops, breakfast cereals, gummy consistent products, chocolate cookies/brownies, hard candies, gelato, gummy bears (65), beef jerky, and even more recently, beer, wine, barley-based sodas, hemp-infused milks, fortified sports products, and health beneficial-honeys (66). There is also infusion of phyto-cannabinoids into liquid fluids such as teas, coffees, citrus-based drinks, and flavored-bottled or oxygenated-bottled waters (66).

In Canada, the federal government has proposed regulations for introducing cannabis edibles and beverages to the legal market (64). Conversely, in the United States, market data have revealed that cannabis edibles have rapidly gained popularity with both medical and recreational consumers (64).

On the other hand, hemp seeds, hemp-seed protein, and hemp-seed oil are considered 'Generally Recognized as Safe' and can be marketed in food without any need for additional approval, so long as they do not make any claims that the ingredients treat disease (66).

Regulatory situation in Portugal

The use of medicinal cannabis is legal in Portugal. The law establishes rules on how to produce, distribute and sell in pharmacies, which will always require a prescription. The decriminalization is controversial and has led to a position by some health professional associations.

Order of Pharmacists position

The Order of Pharmacists issued a statement about the use of cannabis derivatives (67). In their opinion the legislative initiatives are based on general and incorrect assumptions.

It is defended that the two bills proposed by two political parties lack scientific proof not to mention that cannabis has high toxicity potential just as its psychotropic products. There is evidence that cannabis causes the induction of psychosis and schizophrenia, the additive effects and carcinogenicity of smoked cannabis components, as well as various adverse psychotropic effects, some of which are extremely serious, including hallucinations, suicidal thoughts, motor incoordination, distortions in depth perceptions of space and time and endocrine disruption (67).

The Order of Pharmacists corroborates the position of the International Pharmaceutical Federation (FIP), which is strongly opposed to the sale of cannabis for recreational purposes in pharmacies, since pharmacies are health spaces and fosters disease prevention (67).

Thus, the Order of Pharmacists expresses concern about the use of the plant *C. sativa* for medicinal purposes, as there is no scientific evidence to prove the efficacy and safety of its use in the model in which it is intended to be legislated, nor does it add value compared to the drugs already approved and in marketing (68).

Order of Doctors position

The National Council of Medicines Policy of the Order of Doctors issued a statement on the use of cannabis derivatives. In their opinion cannabis should be used as a medicine in situations where there is scientific evidence (69). It is said that current evidence "allows to consider the potential use of cannabis" in some cases (70). However, the opinion indicates that the use of cannabis or cannabinoids as a medicinal product for human use should be subject to "approval by regulatory health authorities" such as the National or European Medicines Authority (70).

The Council also states that no European country authorizes smoked cannabis for medical purposes as it is not sufficiently studied in scientific terms (69), the effects are heterogeneous and they should be object of further studies (71). He also underlines that in other European countries regulation has focused on the use of cannabis preparations, the vast majority of which is not yet marketed in Portugal (72).

Concerning the efficacy of cannabis in clinical use, the Order of Doctors considers that there is strong evidence in the treatment of chronic pain, as an anti-emetic associated with cancer treatment, in the treatment of multiple sclerosis and in the control of anxiety. There is also moderate evidence of cannabis use in improving sleep in people with obstructive sleep apnoea, fibromyalgia, cancer anorexia, and posttraumatic stress disorder. (69)

According to the Portuguese Order of Doctors, medicinal cannabis should be prescribed with a special prescription, such as for morphine derivatives (72). In addition to that, the prescription must state the “identity of the physician, the user, the substance to be administered and the amount” and the requirement that the purchase be made in a pharmacy (73).

Legalization around the world

Considering the therapeutic properties supported by traditional use and some clinical data there has been an evolution for cannabis legalization availability in many countries. Studies in states (e.g., Colorado, California, and Washington) and countries (Uruguay, Portugal, and the Netherlands) where social and legal policies are shifting may provide important data for shaping future policies (34).

For medicinal use

Marijuana was placed in the schedule I category since the Controlled Substances Act of 1970, indicating high potential for abuse and no accepted medical use in the United States. However, in 1992 California was the first state in the union to “legalize” the use of marijuana for medical purposes, and in 2012 Colorado was the first state to pass legislation to allow residents to use marijuana for recreational purposes (44). The legalization of medical marijuana in the United States began in 1996. There are now 10 states (plus the District of Columbia) with legislation to regulate adult use cannabis, 33 states (plus the District of Columbia, Guam, and Puerto Rico)

with legislation to regulate medical cannabis, and 14 states with legislation to regulate high CBD/low THC cannabis products. Only three states (Idaho, South Dakota and Nebraska) allow no form of legal medical cannabis. Despite that the overwhelming majority of states allow some form of medical cannabis, cannabis remains illegal at the federal level (42).

In Europe, it was the Netherlands that became the first country made herbal cannabis available on medical prescription (47). A growing number of other jurisdictions, including Canada, the Netherlands, Israel and the Czech Republic, also have provisions legalising and regulating cannabis for medicinal purposes (74). Israel also allows access to medicinal cannabis (75).

There is also a strong argument for Australia's driving laws to be changed in a way similar to those in Canada, where it is only an offence to have THC in the body whilst driving if the person is also impaired. An alternative of setting a threshold THC limit for a driving under the influence conviction, as was done in Washington State and Colorado in the US, is problematic since how the same doses of THC affect individuals is highly variable. In Colorado, if a driver has five nanograms of active THC in their whole blood, they can be prosecuted for driving under the influence, however law enforcement officers base arrests on observed impairment and 'if a substance has impaired your ability to operate a motor vehicle it is illegal for you to be driving, even if that substance is prescribed or legally acquired'. An independent member for parliament, Fiona Patten, is currently pushing for changes to the state and territory driving laws around THC in Australia (75). The Australian Therapeutic Goods Administration states: '…medicinal cannabis is not considered a first-line therapy for any indication' and 'At this time, we suggest that the use of medicinal cannabis may be considered only when registered medicines have been tried and proven unsuccessful in managing the patient's symptoms or medical condition' (75).

In more than 11 European countries, including the Netherlands, Belgium, and Spain, cannabis is legalized for medicinal use or is decriminalised. Australia joined the list of countries where medicinal cannabis became legal in 2016. Canada legalized medical cannabis in 2001, although accessibility is still restricted and highly regulated through Health Canada. Germany will likely follow suit with medical cannabis (65).

Currently cannabis for therapeutic purposes is already legal in 29 US states but also in Canada and Israel, countries where some of the world's largest producers of the plant are located (6). Canada's arrival of Tilray to Portugal this year, after an Israeli company, has put Portugal on this map (76). According to Infarmed's database, there is currently only one cannabis-based product authorized for commercialization in Portugal, Sativex® a mouthwash solution. It has no reimbursement and comes with the market price of 498€ and is not currently for sale in pharmacies (72).

For recreational use

Canada previously allowed only medicinal use but now allows 'adult use' and Thailand and Malaysia, countries with historically tough drug laws, are considering legalizing cannabis medicinal use. In some countries within Europe such as the Netherlands, 'adult use' is legal, whilst in other countries such as the UK and the Czech Republic, medicinal use when prescribed by a doctor, is permitted (75).

Canada would not be the first nation to consider making recreational cannabis legal. Uruguay, in 2014, became the first country to legalize the sale and distribution of cannabis, where the

government controls the sale through licensed spaces, including pharmacies, and determines the sale price to the public (77).

In 2012, Washington State and Colorado are just two US states that have legalized the recreational use of cannabis. Medical use is legal in over 31 states and districts in the US with some also allowing recreational or 'adult use'. In these states, consumption has been banned in public spaces and limited sale to persons 21 years and older. The product purchase limit ranges from 28 to 224 grams, depending on the state (77).

Many western countries are also considering making cannabis legal for recreational purposes:

- Spanish law prohibits the production, supply and possession of cannabis for personal use in public, but possession in private spaces is not penalized. This allowed the creation of social clubs. Consumers must be members (and there are strict rules for them) and clubs can grow their plants (77).
- In the Netherlands the cultivation, supply and possession of cannabis is not legal. But there is the possibility of consuming in the so-called coffee shops, places of sale and consumption licensed by the municipalities. Legislation prohibits these spaces from advertising, selling to children under 18 or non-residents. Each transaction is limited to five grams (77).

In Portugal

In Portugal criminal penalties of possession of cannabis have been replaced by offenses. If it is intended for personal use, it is limited to 25g of marijuana, 5g of hashish and 2.5g of cannabis oil. The limits are set by 10 daily doses and if exceeded is considered a crime (may be drug use or drug trafficking) (78).

According to the national survey of psychoactive substance use in the general population, prepared by SICAD (Serviço de Intervenção nos Comportamentos Aditivos e nas Dependências), conducted in 2016/17, one in ten Portuguese have used at least cannabis once in their lifetime, with nearly half a million taking this drug in their lifetime. Recreational cannabis is used regularly by about half a million Portuguese, with 2/3 of consumers using it 4 or more times a week, according to the national survey. 15% of consumers who have recently used this drug have high or moderate risk intakes, especially in men aged 15-44. SICAD also notes that "studies conducted in the last 20 years have always shown much higher prevalence of cannabis use than other drugs.". Although recreational cannabis use is not yet legal, the Portuguese find it relatively easy to have access to this drug (78).

The Cannabis Studies Association Cannativa believes that legalizing cannabis for recreational purposes would be "a big step" in combating organized crime and "a step towards public health.". According to them, the regulation would take "people off the street", preventing them from "using a substance in a dangerous, unhealthy place, in contact with dangerous people related to drug trafficking, where there is no strict control over the quality and toxicity of the product". Therefore, it would be a big step in removing business from organized crime groups. Moreover, any consumer who can grow and consume his own cannabis for recreational use, as long as it is not for commercial use, is automatically helping to reduce black market use and reduce revenues from drug trafficking networks, which until now have had business exclusivity (78).

Access to legal cannabis has been correlated to a decrease in opioid requirements. In one study (n=244), cannabis use was associated with a 64% decrease in opioid use, a decrease in side effects of medications and an improved quality of life. This study suggests that many chronic pain patients are substituting opioids for cannabis and reporting greater benefits and fewer side effects. States with legalized cannabis also reported an average 25% decrease in opioid related deaths. The handful of studies and small sample sizes limit generalizability of these data; more studies are needed (42).

Conclusions

Cannabis is probably one of the most commonly used drugs of misuse. On one side it has a wide range of adverse effects including impairing learning and memory. At the same time, the medicinal use of cannabis has been advocated due to its ability to relieve pain, as an example.

It is true that plants have been the historical source of medicine for most of human history and continue to account for the base material of an estimated 25% of modern pharmaceuticals (12). The global prohibition of cannabis cultivation, supply and possession might be considered to present an insurmountable barrier to the full exploration of the therapeutic potential and public health benefits of medicinal cannabis consumption (74). After legalization there is a need for cannabis plant culture and production rules so that they can be used as a safe therapeutic and social basis.

The World Health Organization (WHO) states that, 'Access to essential medicines as part of the right to the highest attainable standard of health ('the right to health') is well founded in international law'. It is a human right. Compassion and a willingness to help alleviate suffering is vital. Patient rights to access medicines of their choice must be taken into consideration by policymakers. Public policy is, by definition, something that should serve the public, not deny them a fundamental human right (11). There is no doubt that a regulated market allows access to quality product and diminish the illicit market.

On the other hand a more fully public health approach to the issue of the therapeutic use of cannabis can be developed (74).

By now we know that cannabinoids have assigned an important therapeutic role in the treatment of symptomatology associated with some types of diseases. Knowing its exact composition, stability and concentration makes its use safer. However, natural cannabinoids may have varied composition and concentration as opposed to synthetic cannabinoids.

As there is no consensus on its medicinal properties, the use of cannabis, as a pharmaceutical and as an 'unapproved therapeutic asset', requires a complex regulatory system as it can be regarded as a drug of dependence or a therapeutic drug (including doctors, other healthcare providers, politicians and consumers) (75).

It is imperative to consider fundamentally what constitutes evidence in Western medicine, since the evidence-based medicine approach is used to make decisions in relation to access to medicines (pharmaceutical and complementary), medical technology and therapeutic modalities (75)

Recognition that there are specific receptors in the brain that recognize cannabinoids and that there are endogenous cannabinoids that act as ligands for these receptors was very important. But there is much to yet to know, for example drug–drug interactions, which are a common cause of adverse reactions and efficacy, it must be investigated among the *Cannabis sativa* molecules (79).

Despite the high availability of *C. sativa* herbal products and their wide beneficial use in medicine, they remain mostly uncharacterized. Establishing common and reasonable grounds for cannabis medical use by promoting the quality and therapeutic activity of herbal or synthetic cannabis products is essential (79).

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